

A brief history of medical diagnosis and the birth of the clinical laboratory

Part 1—Ancient times through the 19th century

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Part 1 in this four-part series was originally published in July 1999.

From tasting urine to microscopy to molecular testing, the sophistication of diagnostic techniques has come a long way and continues to develop at breakneck speed. The history of the laboratory is the story of medicine's evolution from empirical to experimental techniques and proves that the clinical lab is the true source of medical authority.

Three distinct periods in the history of medicine are associated with three different places and, therefore, different methods of determining diagnosis: From the middle ages to the 18th century, bedside medicine was prevalent; then between 1794 and 1848 came hospital medicine; and from that time forward, laboratory medicine has served as medicine's lodestar. The laboratory's contribution to modern medicine has only recently been recognized by historians as something more than the addition of another resource to medical science and is now being appreciated as the seat of medicine, where clinicians account for what they observe in their patients.

The first medical diagnoses made by humans were based on what ancient physicians could observe with their eyes and ears, which sometimes also included the examination of human specimens. The ancient Greeks attributed all disease to disorders of bodily fluids called humors, and during the late medieval period, doctors routinely performed uroscopy. Later, the microscope revealed not only the cellular structure of human tissue, but also the organisms that cause disease. More sophisticated diagnostic tools and techniques—such as the thermometer for measuring temperature and the stethoscope for measuring heart rate—were not in widespread use until the end of the 19th century. The clinical laboratory would not become a standard fixture of medicine until the beginning of the 20th century. This four-part article reviews the history and development of diagnostic methods from ancient to modern times, as well as the evolution of the clinical laboratory from the late 19th century to the present.

Timeline

c. 300 BC Hippocrates advocates examination of urine to diagnose disease.

AD 1267 R. Bacon experiments with optics, probably produces first microscope.

Galen and Hippocrates



c. 1300 Uroscopy is widespread in Europe.

c. 1500 Physicians begin using urine color charts for visual urinalysis.

1590 Hans Janssen invents the compound microscope.

1592 Galileo Galilei invents the thermometer.

1684 Anton van Leeuwenhoek publishes the first drawings of bacteria as seen under the microscope.

1714 Gabriel Fahrenheit develops the mercury thermometer and the Fahrenheit temperature scale.

Ancient diagnostic methods

In ancient Egypt and Mesopotamia, the earliest physicians made diagnoses and recommended treatments based primarily on observation of clinical symptoms. Palpation and auscultation were also used. Physicians were able to describe dysfunctions of the digestive tract, heart and circulation, the liver and spleen, and menstrual disturbances; unfortunately, this empiric medicine was reserved for royalty and the wealthy.

Other less-than-scientific methods of diagnosis used in treating the middle and lower classes included divination through ritual sacrifice to predict the outcome of illness. Usually a sheep would be killed before the statue of a god. Its liver was examined for malformations or peculiarities; the shape of the lobes and the orientation of the common duct were then used to predict the fate of the patient.

Ancient physicians also began the practice of examining patient specimens. The oldest known test on body fluids was done on urine in ancient times (before 400 BC). Urine was poured on the ground and observed to see whether it attracted insects. If it did, patients were diagnosed with boils.

The ancient Greeks also saw the value in examining body fluids to predict disease. At around 300 BC, Hippocrates promoted the use of the mind and senses as diagnostic tools, a principle that played a large part in his reputation as the “Father of Medicine.” The central Hippocratic doctrine of humoral pathology attributed all disease to disorders of fluids of the body. To obtain a clear picture of disease, Hippocrates advocated a diagnostic protocol that included tasting the patient’s urine, listening to the lungs, and observing skin color and other outward appearances. Beyond that, the physician was to “understand the patient as an individual.” Hippocrates related the appearance of bubbles on the surface of urine specimens to kidney disease and chronic illness. He also related certain urine sediments and blood and pus in urine to disease. The first description of hematuria, or the presence of blood in urine, by Rufus of Ephesus surfaced at around AD 50 and was attributed to the failure of kidneys to function properly in filtering the blood.

Later (c. AD 180), Galen (AD 131–201), who is recognized as the founder of experimental physiology, created a system of pathology that combined Hippocrates’ humoral theories with the Pythagorean theory, which held that the four ele-

ments (earth, air, fire and water), corresponded to various combinations of the physiologic qualities of dry, cold, hot and moist. These combinations of physiologic characteristics corresponded roughly to the four humors of the human body: hot + moist = blood; hot + dry = yellow bile; cold + moist = phlegm; and cold + dry = black bile.

Galen was known for explaining everything in light of his theory and for having an explanation for everything. He also described diabetes as “diarrhea of urine” and noted the normal relationship between fluid intake and urine volume. His unwavering belief in his own infallibility appealed to complacency and reverence for authority. That dogmatism essentially brought innovation and discovery in European medicine to a standstill for nearly 14 centuries. Anything relating to anatomy, physiology and disease was simply referred back to Galen as the final authority from whom there could be no appeal.

Middle Ages

In medieval Europe, early Christians believed that disease was either punishment for sin or the result of witchcraft or possession. Diagnosis was superfluous. The basic therapy was prayer, penitence, and invocation of saints. Lay medicine based diagnosis on symptoms, examination, pulse, palpitation, percussion, and inspection of excreta and sometimes semen. Diagnosis by “water casting” (uroscopy) was practiced, and the urine flask became the emblem of medieval medicine. By AD 900, Isaac Judaeus, a Jewish physician and philosopher, had devised guidelines for the use of urine as a diagnostic aid; and under the Jerusalem Code of 1090, failure to examine the urine exposed a physician to public beatings. Patients carried their urine to physicians in decorative flasks cradled in wicker baskets and, because urine could be shipped, diagnosis at long distance was common. The first book detailing the color, density, quality and sediment found in urine was written around this time, as well. By around AD 1300, uroscopy became so widespread that it was at the point of near universality in European medicine.

Medieval medicine also included interpretation of dreams in its diagnostic repertoire. Repeated dreams of floods indicated “an excess of humors that required evacuation,” and dreams of flight signified “excessive evaporation of humors.”

1754 Leopold Auenbrugger introduces percussion of the chest into medical diagnosis.

1770 John Hill introduces a method of obtaining specimens for microscopic study.

1789 de Fourcroy discovers cholesterol.

Uroscopy in an early physician's office



1816 R. T. H. Laennec invents the stethoscope; G. B. Amici invents the dioptric/achromatic microscope.

1828 British hospitals are organized into clinical wards.

1830 Gerardus Mulder performs the first elemental chemical analysis of proteins; J. J. Lister develops an achromatic microscope and introduces dark-field microscopy.

1836 James Marsh develops a standard test for arsenic.

Seventeenth century

The medical advances of the 17th century consisted mostly of descriptive works of bodily structure and function that laid the groundwork for diagnostic and therapeutic discoveries that followed. The status of medicine was helped along by the introduction of the scientific society in Italy and by the advent of periodical literature.

Considered the most momentous event in medical history since Galen's time, the discovery of the circulation of blood by William Harvey (1578–1657) marked the beginning of a period of mechanical explanations for a variety of functions and processes, including digestion, metabolism, respiration and pregnancy. The English scientist proved through vivisection, ligation and perfusion that the heart acts as a muscular pump propelling the blood throughout the body in a continuous cycle.

The invention of the microscope opened the door to the invisible world just as Galileo's telescope had revealed a vast astronomy. The earliest microscopist was a Jesuit priest, Athanasius Kircher (1602–1680) of Fulda (Germany), who was probably the first to use the microscope to investigate the causes of disease. His experiments showed how maggots and other living creatures developed in decaying matter. Kircher's writings included an observation that the blood of patients with the plague contained "worms;" however, what he thought to be organisms were probably pus cells and red blood corpuscles because he could not have observed *Bacillus pestis* with a 32-power microscope. Robert Hooke (1635–1703) later used the microscope to document the existence of "little boxes," or cells, in vegetables and inspired the works of later histologists; but some of the greatest contributions to medical science came from Italian microscopist, Marcello Malpighi (1628–1694).

Malpighi, who is described as the founder of histology, served as physician to Pope Innocent XII and was famous for his investigations of the embryology of the chick and the histology and physiology of the glands and viscera. His work in embryology describes the minutiae of the aortic arches, the head fold, the neural groove, and the cerebral and optic vesicles.

Uroscopy was still in widespread use and had gained popularity as a method to diagnose "chlorosis," or love-sick young women, and sometimes to test for chastity. Other methods of urinalysis had their roots in the 17th century, as well.

1841 P. S. Denis describes the separation of blood proteins into albumins and globulins by salt precipitation.

1846 The optical factory of Carl Zeiss is founded in Jena, Germany.

1847 The American Medical Association is founded.

Early stethoscopes



The gravimetric analysis of urine was introduced by the Belgian mystic, Jean Baptiste van Helmont (1577–1644). Van Helmont weighed a number of 24-hour specimens, but was unable to draw any valuable conclusions from his measurements. It was not until the late 17th century—when Frederik Dekkers of Leiden, Netherlands, observed in 1694 that urine that contained protein would form a precipitate when boiled with acetic acid—that urinalysis became more scientific and more valuable. The best qualitative analysis of urine at the time was pioneered by Thomas Willis (1621–1675), an English physician and proponent of chemistry. He was the first to notice the characteristic sweet taste of diabetic urine, which established the principle for the differential diagnosis of diabetes mellitus and diabetes insipidus.

Experiments with blood transfusion were also getting underway with the help of a physiologist in Cornwall, England, named Richard Lower (1631–1691). Lower was the first to perform direct transfusion of blood from one animal to another. Other medical innovations of the time included the intravenous injection of drugs, transfusion of blood, and the first attempts to use pulse rate and temperature as indicators of health status.

Eighteenth century

The 18th century is regarded as the "Golden Age" of the successful practitioner, as well as the successful quack. Use of phrenology (the study of the shape of the skull to predict mental faculties and character), magnets, and various powders and potions for treatment of illness were a few of the more popular scams. The advancement of medicine during this time was more theoretical than practical. Internal medicine was improved by new textbooks that cataloged and described many new forms of disease, as well as by the introduction of new drugs, such as digitalis and opium. The state of hospitals in the 18th century, however, was alarming by today's standards. Recovery from surgical operations was rare because of septicemia. The concept of antisepsis had not yet been discovered, and hospitals were notorious for filth and disease well into the 19th century.

One notable event that is a forerunner to the modern practice of laboratory measurement of prothrombin time, plasma thromboplastin time and other coagulation tests, was the discovery of the cause of coagulation. An English physiologist, William Hewson (1739–1774) of Hexham, Northumberland, England, showed that when the coagulation of

1849 A. E. Berthold demonstrates endocrine function by proving that the testes are required in roosters for comb growth.

1852 K. Vierordt develops a method

for performing accurate blood counts (hemocytometry); G. G. Stokes discovers fluorescence.

1854 John Snow links London cholera outbreak to Broad Street Pump; Jules Duboscq develops the first visual colorimeter based on Beer's Law.

1856 William Perkin prepares the first synthetic dye.

Table

Evolution of diagnostic tests as documented in textbooks of laboratory medicine

Copyright year	Author, Title	New tests described
1892	Sir William Osler, <i>Textbook of Medicine</i>	Hemoglobin estimation, red and white blood cell counts, malaria parasite identification, simple urinalysis, examination of sputum for tuberculosis.
1898	Sir William Osler, <i>Textbook of Medicine</i>	Blood culture, agglutination test for typhoid fever, isolation of Klebs-Löffler bacillus with virulence tests in diphtheria, lumbar puncture, examination of cerebrospinal fluid in suspected meningitis, amino aciduria in liver disease.
1901	Sir William Osler, <i>Textbook of Medicine</i>	Isolation of typhoid bacilli from urine and the clotting time in hemophilia.
1912	Sir William Osler, <i>Textbook of Medicine</i>	Tissue examination for spirochetes in syphilitic lesions, the Wassermann test, osmotic fragility tests, a crude form of the glucose tolerance test.
1914	P. N. Panton (title N/A)	Blood counts and examination of stained smears, agglutination reactions, the Wassermann test, parasitology, blood cultures, spectroscopic examination, visual detection of bilirubinemia, Gmelin tests, Garrod technique for uric acid, alkalinity of blood, bacteriology (basic staining and culture methods in use today), urinalysis (pus, red blood cells, albumin, sugar), test meals in use, fecal examinations for fat and sterocobilin, histology (frozen section and paraffin embedding).

the blood is delayed, a coagulable plasma can be separated from the corpuscles and skimmed off the surface. Hewson found that plasma contains an insoluble substance that can be precipitated and removed from plasma at a temperature slightly higher than 50°C. Hewson deduced that coagulation was the formation in the plasma of a substance he called “coagulable lymph,” which is now known as fibrinogen. A later discovery that fibrinogen is a plasma protein and that in coagulation it is converted into fibrin attests to the importance of Hewson’s work.

The clinical diagnostic methods of percussion, temperature, heart rate and blood pressure measurements were further refined, and there were some remarkable attempts to employ precision instruments in diagnosis.

Leopold Auenbrugger (1722–1809) was the first to use percussion of the chest in diagnosis in 1754 in Vienna. This method involved striking the patient’s chest while the patient holds his or her breath. Auenbrugger proposed that the chest

of a healthy person sounds like a cloth-covered drum. A student of Auenbrugger’s, Jean Nicolas Corvisart, a French physician at La Charité in Paris, pioneered the accurate diagnosis of heart and lung diseases using Auenbrugger’s chest-thumping technique. Corvisart’s translation of Auenbrugger’s treatise on percussion, “*New Invention to Detect by Percussion Hidden Diseases in the Chest,*” popularized the practice of thumping on a patient’s chest. The resulting sounds are different when the lungs contain lesions or fluids than in healthy people. This observation was validated by post-mortem examination.

James Currie (1756–1805), a Scot, was the first to use cold baths in treatment of typhoid fever; and by monitoring the patient’s temperature using a thermometer, he was able to adjust the temperature and frequency of the baths to treat individual patients. It took another hundred years, however, before thermometry became a recognized feature in clinical diagnosis.



1859 E. Becquerel invents the fluorescent lamp.

1866 Voit establishes the first hygienic laboratory in Munich.

Uroscopy

1869 Luer invents the glass hypodermic syringe.

1871 The dry-plate photographic process is invented.

1872 Oscar Brefeld develops the use of a gelatin medium for isolation of fungi in pure culture.

1875 Corfield establishes the first public health laboratory in England; Osaka, Japan, establishes the Imperial Hygienic Laboratory.

1879 Karl von Linde invents the domestic refrigerator; Thomas Edison invents the incandescent light bulb.

1886 Jaffe develops alkaline picrate method for the determination of creatinine;

In 1707, Sir John Floyer (1649–1734) of Staffordshire, England, introduced the concept of measuring pulse rate by timing pulse beats with a watch. He counted the beats per minute, and tabulated the results; but his work was ignored because of a healthy skepticism for an old Galenic doctrine of there being a special pulse for every disease.

The groundbreaking work for measuring blood pressure was done by Stephen Hales (1677–1761), an English clergyman. By fastening a long glass tube inside a horse's artery, Hales devised the first manometer or tonometer, which he used to make quantitative estimates of the blood pressure, the capacity of the heart and the velocity of blood current. Hales' work was the precursor for the development of the sphygmomanometer used today to measure arterial blood pressure.

Additional advances in urinalysis occurred with J.W. Tichy's observations of sediments in the urine of febrile patients (1774); Matthew Dobson's proof that the sweetness of the urine and blood serum in diabetes is caused by sugar (1776); and the development of the yeast test for sugar in diabetic urine by Francis Home (1780).

Nineteenth century

The emergence of sophisticated diagnostic techniques and the laboratories that housed them coincides roughly with the worldwide political, industrial and philosophical revolutions of the 19th century, which transformed societies dominated by religion and aristocracy into those dominated by the industrial, commercial and professional classes. In the decades after the Civil War, American laboratories and their champions were met with a vehement skepticism of science, which was viewed by some as an oppressive tool of capitalist values. The lay public, as well as many practitioners, saw the grounding of medicine in the laboratory as a removal of medical knowledge from the realm of common experience and as a threat to empiricism. Many American physicians who went abroad to Germany and France for supplementary training came back to impart the ideals of European medicine, as well as those of higher education for its own sake, to an American society that found these beliefs threatening. The lab itself was not seen as a threat, but rather the claims it made to authority over medical practice were assailed. The empiricists and the "speculative medical experimentalists" were for the most part divided along generational lines. The older empiricists had a stake in continuing their careers independent of a medical infrastructure or system, while the

younger physicians aspired to careers in academic medical centers patterned after German institutions. The younger, more energetic ranks had to first lobby for such facilities to be built; and as older doctors retired from teaching posts and turned over editorship of scientific journals, this opposition to the lab faded.

Medical historians also note that the 19th century was one in which the rest of therapeutics lagged behind, and called it an era of public health. New discoveries in bacteriology allowed for water treatment and pasteurization of milk, which significantly decreased mortality rates. In addition, the advent of antiseptic surgery in the late 19th century reduced the mortality from injuries and operations and increased the range of surgical work. Medical practitioners relied, for a time, more on increased hygiene and less on drugs. Advances in public and personal hygiene had dramatically improved the practice of medicine; predictions were even made that the pharmacopoeia of the time would eventually be reduced to a small fraction of its size.

At the beginning of the century, physicians depended primarily on patients' accounts of symptoms and superficial observation to make diagnoses; manual examination remained relatively unimportant. By the 1850s, a series of new instruments, including the stethoscope, ophthalmoscope and laryngoscope, began to expand the physician's sensory powers in clinical examination. These instruments helped doctors to move away from a reliance on the patients' experience of illness and gain a more detached relationship with the appearance and sounds of the patients' body to make diagnoses.

Another wave of diagnostic tools—including the microscope and the X-ray, chemical and bacteriological tests, and machines that generated data on patients' physiological conditions, such as the spirometer and the electrocardiograph—produced data seemingly independent of the physician's as well as the patient's subjective judgment. These developments had uncertain implications for professional autonomy: They further reduced dependence on the patient, but they increased dependence on capital equipment and formal organization of medical practice.

These detached technologies added a highly persuasive rhetoric to the authority of medicine. They also made it possible to move part of the diagnostic process behind the scenes and away from the patient where several physicians could have simultaneous access to the evidence. The stethoscope,



The Pasteur Institute is founded in Paris.

1890 The Royal College of Physicians

Binocular microscope with light collector c.1870

and Surgeons establishes a conjoint clinical laboratory in London; G. S. Woodhead is the first director.

1891 C. E. Brown-Sequard describes "internal secretions" as produced by specific organs.

1892 J. Dewar invents the vacuum flask; Charles and William Mayo found their

clinic and hire colleagues to perform laboratory testing; New York City Department of Health establishes the first public diagnostic bacteriology lab in the U.S. under Hermann N. Biggs and William H. Park; Laboratory of Hygiene at the University of Pennsylvania is opened in Philadelphia.

A brief history of the hospital

The earliest hospitals in pre-industrial societies were charitable institutions used for tending the sick as opposed to medical institutions that provided for their cure. Medieval hospitals were operated by religious or knightly orders in individual communities. The facility was essentially a religious house in which the nursing personnel had united as a vocational community under a religious rule.

In colonial America, almshouses were the first institutions to provide care for the sick. These facilities also had a communal character in that they provided a substitute residence for people who were homeless, poor, or sick. Founded as early as the 17th century in America, almshouses offered sanctuary to all kinds of dependent people from the elderly to the orphaned, the insane, the ill, and the debilitated. In a number of large cities, hospitals evolved from almshouses: The Philadelphia Almshouse became Philadelphia General Hospital; the New York Almshouse became Manhattan's Bellevue Hospital; and the Baltimore County Almshouse became part of the Baltimore City Hospitals.

The next rendition of the hospital was a facility that served the sick but limited its services to the poor. Not until the 19th century did hospitals serving all classes emerge. The Daughters of Charity Medical Center in New Orleans was founded in 1734, making it the oldest hospital in the United States. New York Hospital was chartered in 1717, but wasn't opened for another 20 years, and the Massachusetts General Hospital opened in Boston in 1821. These institutions were termed "voluntary" because they were financed with donations, rather than with taxes.

In Europe, hospitals figured prominently in medical education and research, but were mostly ignored in America until the founding of Johns Hopkins. Between 1870 and 1910, however, hospitals began to play this part in the United States, as well.

Before 1900, the hospital offered no special advantages over the home in terms of surgery. The infections that periodically swept through the wards made physicians cautious about sending patients there. Antiseptic techniques were for a short time adapted for use in patients' homes. "Kitchen surgery" became more inconvenient for patient and surgeon alike as procedures became more demanding and more people moved into apartments. As antiseptic techniques improved, and the stigma of disease in the hospital died out, surgery was brought back into the hospital.

Source: Starr P. *The Social Transformation of American Medicine*. New York: Basic Books Inc.; 1982.

for example, could only be used by one person at a time, but lab tests and X-rays enabled several doctors to view and discuss the results. This team approach to diagnosis strengthened the medical community's claim to objective judgment. Equipped with methods for measuring, quantifying and qualifying, doctors could begin to set standards of human physiology, evaluate deviations, and classify individuals.

Microscopy

Many scientists were making great strides in bacteriology, microbiology, and histology as well. Improvements in the microscope allowed further exploration of the cellular and microbial worlds in the 19th century. Johannes Evangelista Purkinje was an important Bohemian pioneer of the use of the microscope. In 1823, he was appointed professor of physiology at the University of Breslau; and a year later, he

started a physiologic laboratory in his own house. Purkinje's work includes descriptions of the germinal vesicle in the embryo, description and naming of protoplasm, discovery of the sudoriferous glands of the skin and their excretory ducts, and numerous descriptions of brain, nerve, and muscle cells.

When John Snow studied the great London cholera outbreak in 1854, he brought it under control by tracing it to the Broad Street Pump and eliminating access to this source of contaminated water. Snow's work foreshadowed some of the earliest successful applications of laboratory methods to public hygiene that came in the 1860s and 1870s with the breakthroughs in bacteriology made by Louis Pasteur and Robert Koch.

Louis Pasteur (1822–1895) discovered the anaerobic character of the bacteria of butyric fermentation and introduced

1893 J. Elster and H. F. Geitel invent the photoelectric cell; T. W. Richards invents the nephelometer; Hermann M. Biggs establishes Diagnostic Laboratory in New York City.

1895 Franz Ziehl and Friedrich Neelsen introduce their modification of the acid-fast stain for tuberculosis; William Roentgen discovers X-rays; William

Pepper Laboratory is established at the Pennsylvania General Hospital.

1896 S. Riva-Rocci invents the sphygmomanometer; C. W. Purdy publishes *Practical Urinalysis and Urinary Diagnosis*; Ferdinand Widal develops the agglutination test for identification of the typhoid bacillus; in Great Britain, clinical laboratories existed in Edinburgh, Leeds,

Glasgow, and London by this date.

1897 The first commercial clinical laboratory established in England, The Clinical Research Association, receives specimens by mail.

Source: CLMA and Garrison. Portions of this timeline are reprinted with permission from CLMA.

*In the 19th century,
diagnostic tools—
including the microscope and
X-ray—helped provide hard
data independent of subjective
judgment and anecdote.*

the concepts of aerobic and anaerobic bacteria around the year 1861. About the same time, he discovered that the pellicle that is necessary in the formation of vinegar from wine consists of a rod-like microorganism, *Mycoderma aceti*. In 1867, the wine industry of

France reported a significant gain in revenue because of Pasteur's discovery that the spoiling of wine by microorganisms can be prevented by partial heat sterilization (Pasteurization) at a temperature of 55–60°C without any alteration of the taste. Later (c. 1878), an accident brought about the discovery of preventive inoculation with the weakened form of a virus. While Pasteur was away on vacation, virulent cultures of chicken cholera became inactive; and when injected into animals, they were found to act as preventive vaccines against a subsequent injection of a live organism. The attenuated virus could be carried through several generations and still maintain its immunizing property. In 1881, Pasteur produced a vaccine against anthrax and lowered the mortality rate to 1% in sheep and to 0.34% in cattle. In 1885, the Pasteur Institute was opened, and here Pasteur worked with several protégés for the rest of his life.

A contemporary of Pasteur's, Robert Koch (1843–1910), began a brilliant career and a series of discoveries with his report in 1876 on the complete life history and sporulation of the anthrax bacillus. His culture methods were confirmed by Pasteur; and in 1877, Koch published his methods of fixing and drying bacterial films on coverslips, of staining them with Weigert's aniline dyes, of staining flagella, and of photographing bacteria for identification and comparison. The following year, he published a memoir that included an etiology of traumatic infectious disease in which the bacteria of 6 different kinds of surgical infection are described, with the pathological findings of each microorganism breeding true through many generations *in vitro* or in animals. In 1881, he developed a method of obtaining pure cultures of organisms by spreading liquid gelatin with meat infusion on glass plates, forming a solid coagulum. Koch also played a role in perfecting the method of steam sterilization. The year after that, he discovered the tubercle bacillus by other special culture and staining methods and formulated a rule for determining the specificity of disease-causing organisms. The rule, called Koch's postulates or Koch's law, stipulated that the specificity of a pathogenic microorganism could only be established if: (1) it is present in all cases of the disease, (2) inoculations of its pure cultures produce disease in animals, (3) from these cultures it can again be obtained, and (4) then it can again be propagated in pure cultures. In 1883, Koch discovered *Cholera vibrio* and recognized its routes of transmission as drinking water, food and clothing. In 1893, he wrote an important paper on waterborne epidemics showing how they could be prevented by proper filtration. Finally, in 1905,

Koch received the Nobel Prize.

These two bacteriologists were responsible for the isolation of the organisms responsible for major infectious diseases and led public health officials to make more focused efforts against specific diseases. Sand filtration of the water supply

was introduced in the 1890s and proved to be effective in preventing typhoid. Regulation of the milk supply also cut infant mortality dramatically. Antiseptic surgery, which reduced the mortality from injuries and operations and increased the range of surgical work, represents another successful application of the work of these two scientists.

The emergence of quantitative diagnosis and the hospital laboratory

By the mid-1800s, lab tests had been introduced to detect tuberculosis, cholera, typhoid and diphtheria, but cures for these diseases would not come until later. Physicians also began to study pulse, blood pressure, body temperature and other physiological indicators, even though simple, practical instruments to measure these signs were not developed until the end of the century. The use of precise measurements in diagnosis became standard in medicine in the early 1900s. Standardized eye tests, weight and height tables, and IQ tests were all part of a movement to identify statistical norms of human physiology and behavior.

The first hospital lab in Britain, which was set up at Guys Hospital, was organized into clinical wards. Two of these wards were designated for medical student rotations and had a small laboratory attached for clinical work. By 1890, most laboratory procedures in the United States were performed by the physician with a microscope in his home or office. In 1898, Sir William Osler, a Canadian physician, professor, and one of the first well-known authors in the clinical laboratory literature, established ward laboratories at Johns Hopkins Hospital, where routine tests were carried out by attending physicians, and more complex procedures and research problems were referred to the pathology laboratory.

An increasing number of useful laboratory tests were discovered in the second half the 1800s, and by the turn of the century, specific chemical and bacteriological tests for disease emerged rapidly. In the 1880s, the organisms responsible for tuberculosis, cholera, typhoid and diphtheria were isolated; and by the mid-1890s, lab tests had been introduced to detect these diseases. The spirochete that causes syphilis was identified in 1905; the Wassermann test for syphilis was introduced in 1906. Advances in the analysis of urine and blood gave physicians additional diagnostic tools. These innovations were the result of progress in basic science that made it possible to duplicate successful applications more rapidly than ever before. The earlier advances in

immunization, such as smallpox vaccination, had been purely empirical discoveries and were not quickly repeated. Microbiology for the first time enabled physicians to link disease-causing organisms, symptoms and lesions systematically. The principles that Pasteur demonstrated in the development of anthrax and rabies vaccines now provided a rational basis for developing vaccines against typhoid, cholera and plague.

Surgery

Surgery enjoyed tremendous gains in the late 1800s. Before anesthesia, surgery required brute force and speed because it was important to get in and out of the body as quickly as possible. After William T. G. Morton's (1819–1868) demonstration of ether at the Massachusetts General Hospital in 1846, use of anesthesia allowed for slower and more careful operations. Joseph Lister's (1827–1912) methods of antiseptics using carbolic acid, first published in 1867, became general practice around 1880 and improved the previously grim mortality rates for all types of surgery. Before antiseptic techniques, the mortality rate for amputations was about 40%. Surgeons were reluctant to penetrate the major bodily cavities, and then only as a last resort. After surgeons were able to master the tedious procedures demanded in antiseptics, they began to explore the abdomen, chest and skull and developed specific techniques for each area. The sophistication and success of surgery blossomed in the 1890s and early 1900s, spurred on by the development of X-rays in 1895. Surgeons were able to operate earlier and more often for a variety of ills, including appendicitis, gall bladder disease and stomach ulcers. The growth in surgical work provided a means for expanding profit in hospital care as well (see *Sidebar*, "A brief history of the hospital").

Hematology

In the later part of the century, several discoveries emerged as the foundation of hematologic methods. In 1877, K.

Vierordt introduced coagulation time as an index of blood coagulative power. Sir Almroth Edward Wright, an Irish professor of pathology in Dublin, was the first to observe the role of calcium salts in the coagulation of blood. He also devised a coagulometer to estimate coagulation time. In 1879, Paul Ehrlich (1854–1915), a Czech cellular pathologist and chemist, was enamored with dyes and developed many methods of drying and fixing blood smears using heat. Ehrlich also discovered mast cells and saw their granulations using a basic aniline stain. His classification of white blood cells into different morphological types (neutrophilic, basophils and oxyphilic) paved the way for identifying many diseases of the blood. Ehrlich also contributed to microbiology the discovery of methylene blue as a bacterial stain. □

Editor's note:

A review of diagnostic technology and discovery from ancient times to the nineteenth century establishes the emergence and popularization of laboratory medicine at about 1850. The advent of antiseptic surgery, as well as public and personal hygiene, attest to the benefits that other branches of medicine have enjoyed as a direct result of the efforts of laboratory scientists during this period. Part 2 of this series explores the development of modern clinical chemistry, as well as takes a retrospective look at the ever-changing regulatory landscape in the United States.

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